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CITATIONS

Cases:

In the Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-555

CASPAR W. WEINBERGER, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS, PETITIONERS

v.

BENTEX PHARMACEUTICALS, INC., ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

BRIEF FOR PETITIONERS

OPINIONS BELOW

The opinion of the court of appeals (J.A. 258-270[1]) is reported at 463 F. 2d 363. The opinion of the district court (J.A. 251-258) is not officially reported.

JURISDICTION

The judgment of the court of appeals (J.A. 270) was entered on May 23, 1972. Mr. Justice Rehnquist extended the time within which to file a petition for

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[1] "J.A." refers to the Joint Appendix filed by the parties in this case and in Nos. 72-394, 72-414, 72-528, and 72-666, with which this case has been consolidated.

a writ of certiorari to October 5, 1972. The petition was filed on that date and was granted on January 8, 1973 (J.A. 271). The jurisdiction of this Court rests on 28 U.S.C. 1254(1).

QUESTION PRESENTED

Whether the Food and Drug Administration has jurisdiction to determine initially whether a product is a "new drug" which must be administratively approved as safe and effective before it can be sold in commerce.

STATUTES INVOLVED

Relevant provisions of the Federal Food, Drug, and Cosmetic Act, 52 Stat. 1040, as amended by the Harris-Kefauver Act, 76 Stat. 780, 21 U.S.C. 301 *et seq.*, and of the Administrative Procedure Act, 5 U.S.C. 551–559, 701–706, are set forth in the Joint Appendix (J.A. 475–487).

STATEMENT

This is one of five consolidated cases now pending before the Court involving the interpretation of, and the procedures to be followed in implementing, the effectiveness provisions of the 1692 amendments to the Federal Food, Drug, and Cosmetic Act of 1938 (76 Stat. 780–786).[2] These five cases present interrelated

[2] The other cases are: *Weinberger* v. *Hynson, Westcott and Dunning, Inc.*, No. 72–394; *Hynson, Westcott and Dunning, Inc.* v. *Weinberger*, No. 72–414 (cross-petition); *CIBA Corporation* v. *Weinberger*, No. 72–528; and *USV Pharmaceutical Corporation* v. *Weinberger*, No. 72–666. On January 8, 1973, this Court granted the petitions for writs of certiorari in all five cases, consolidated them, and allotted a total of three hours for argument.

and overlapping issues. We are therefore setting forth, in this brief, a general discussion of the historical background of drug marketing regulation, the statutes involved, and the efforts of the Food and Drug Administration ("FDA") to implement the congressional directives relating to drug efficacy, in order to provide a background against which the issues involved in all five cases may be assessed.

I. STATUTORY AND ADMINISTRATIVE BACKGROUND

A. THE FEDERAL FOOD, DRUG, AND COSMETIC ACT OF 1938

Until 1938, federal law did not provide for any kind of administrative pre-marketing approval for pharmaceuticals sold in interstate commerce. The Food and Drug Act of 1906, 34 Stat. 768, prohibited introduction into commerce of adulterated and misbranded drugs, narrowly defined, and provided only criminal sanctions and seizure by libel for condemnation. The Secretary of Agriculture was authorized to conduct hearings concerning particular products, but only for the purpose of certifying violations to the United States Attorney.

In 1938, however, spurred by a tragedy resulting from the marketing of an untested, toxic drug,[3] Con-

[3] The product was "Elixir Sulfanilamide." The manufacturer combined sulfanilamide, a useful drug usually administered in tablet or powder form, with diethylene glycol, an extremely toxic solvent (now used mainly as antifreeze). The company marketed this new product without first testing it for safety. During September and October of 1937, at least 73 persons died as a direct result of taking "Elixir Sulfanilamide." Dunn, *Federal Food, Drug and Cosmetic Act* (1938), pp. 1316–1327; S. Doc. No. 124, 75th Cong., 2d Sess. (1937).

gress provided in the Federal Food, Drug and Cosmetic Act, 52 Stat. 1040, for regulatory clearance of drugs prior to marketing[4] and for administrative suspension of such clearance if thereafter required for public safety. The statute established a scheme which prohibited the introduction of "any new drug" in interstate commerce unless an application filed with the Secretary of Agriculture[5] was "effective with respect to such drug." Section 505(a), 52 Stat. 1052.[6] Such "new drug applications" are known as "NDAs". A "new drug" was defined as "[a]ny drug the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe" for its intended use. Section 201(p), 52 Stat. 1041–1042.[7] The application was automatically to become effective within a fixed period unless the Secretary, after notice and opportunity for hearing, refused to permit it to become effective after finding that he could not determine from existing evidence,

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[4] See H. Rep. No. 2139, 75th Cong., 3d Sess. (1938); Dunn, *supra*, at 817, 823.

[5] The functions of the Secretary of Agriculture under the Act were assigned to the Food and Drug Administration, which was transferred in 1940 to the Federal Security Agency, and in 1953 to the Department of Health, Education and Welfare. The Secretary of the latter Department has delegated his authority under the Act to the Commissioner of Food and Drugs. 21 C.F.R. 2.120. See note following 21 U.S.C. 321 at p. 5421.

[6] Sections 201(p) and 505(a)–(e) of the 1938 Act are set forth at J.A. 482–484.

[7] A grandfather clause exempted drugs subject to the 1906 Act whose labeling had not been changed. Section 201(p)(1), 52 Stat. 1042.

or had not been shown, that the drug was safe. Sections 505(c) and (d), 52 Stat. 1052. Any NDA in effect could be suspended, after notice and opportunity for hearing, if clinical experience or new testing methods showed that the drug was not safe. Section 505(e), 52 Stat. 1053. Orders denying or suspending an NDA were reviewable on the administrative record in the district courts. Section 505(h), 52 Stat. 1053.

This regulatory authority was supplemented by the Act's general administrative provisions authorizing the Secretary to promulgate regulations for the efficient enforcement of the Act, and to conduct examinations, inspections and investigations and publish the results. Sections 701–705, 52 Stat. 1055–1058. In addition, judicial sanctions were authorized to enforce the Act's administrative requirements. The marketing of a "new drug" without an effective NDA could be enjoined or be made the basis of a criminal prosecution, or the drug involved could be seized in libel and condemnation proceedings.[8] The Act also provided for the same judicial sanctions to be applied to the sale of misbranded drugs—*i.e.,* drugs for which the labeling is false or misleading.[9]

B. FDA'S IMPLEMENTATION OF THE 1938 ACT AND THE "ME-TOO" PROBLEM.

The agency's administration of the Act was directly affected by three factors: the enormous number of

[8] Sections 301(d), 302(a), 303, 304 (21 U.S.C. (1958 ed.) 331(d), 332(a), 333, 334).

[9] Sections 502(a), 301(a), 302, 303, 304 (21 U.S.C. (1958 ed.) 352a, 331(a), 332(a), 333, 334).

new drug applications it was required to review, in relation to its limited resources; the absence of any requirement that manufacturers and packagers register drugs with the agency before or after putting them on the market; and FDA's lack of power, in determining whether to permit an NDA to become effective, to consider whether products which were safe were also therapeutically efficacious.

From the outset, the Food and Drug Administration received a swelling stream of new drug applications supported by voluminous data.[10] To cope with this problem, which was aggravated by war-related staff shortages, the agency adopted the practice in 1942 of examining each application to determine whether the product was in fact a new drug, and of advising the manufacturer of its determination. By 1949, the Commissioner was able to report that the "growing disposition on the part of the drug industry to ask the opinion of the Food and Drug Administration in advance as to the status of proposed new products * * * has led to a steady decline in applications ruled not new drugs."[11] Nevertheless, in the twenty-four years between 1938 and 1962 the number and total sales of "new drugs" on the market had grown enormously.[12]

[10] By June 30, 1939, the agency had received 1,277 NDAs. 1939 Annual Report of the Food and Drug Administration, reprinted in Federal Food, Drug, and Cosmetic Law Administrative Reports—1907–1949 (hereafter "Admin. Reps.") at 927; by 1941 the number filed had increased to 4,128. *Id.* at 1006.

[11] Admin Reps. at 1415.

[12] Expenditures for drugs increased from $1.8 billion in 1951 to more than $5 billion in 1962. Annual Reports of the U.S. Department of Health, Education, and Welfare (1961) at 315,

By June 30, 1962, the agency had permitted 9,457 NDAs to become effective, as well as some 12,000 supplemental NDAs for labeling, manufacturing and formulation changes on articles previously covered.[13]

In addition to products for which an NDA had become effective, however, there were many thousands of similar or identical formulations for which the manufacturer had not filed an application. These manufacturers either concluded that their products were generally recognized as safe because an NDA was in effect for the drug they imitated, marketed their products illegally without being discovered, or received an advisory opinion letter from the agency that an NDA was not required because their product was generally recognized among experts as safe.[14] Such products are known as "me-too" drugs.[15] While the precise number

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(1963) at 285. In 1954 the Secretary reported that: "In the drug field at least half of the drugs in prominent use today were unknown when the Food, Drug, and Cosmetic Act was enacted. All of the antibiotics and all but one of the sulfonamides have achieved their present widespread use since 1938. Whereas 10 million dollars' worth of endocrines were produced in 1939, the output had grown to $90 million in 1952, and new products such as cortisone and ACTH had entered the picture." Annual Report of U.S. Department of Health, Education, and Welfare (1954) at 193.

[13] See Annual Reports of the Federal Security Agency (1938–1952); Annual Reports of the U.S. Department of Health, Education, and Welfare (1953–1962). The Food and Drug Administration estimates that of the 5,737 NDAs that became effective between 1950 and 1962, approximately 1,500 were for veterinary products.

[14] Such "not new drug" letters were issued when one or more NDAs were already effective on similar drugs.

[15] See Hearings on Drug Listing Act, 1971, before the Senate Committee on Labor and Public Welfare, 92d Cong., 1st Sess., at 18, 21–22.

of all such identical or related drugs has not been ascertained, it was estimated in 1969 that for every NDA drug there are five identical or similar drugs.[16] FDA's experience to date indicates that this estimate is low. FDA has found an average ratio of 13 similar or "me-too" drugs for each NDA drug withdrawn from the market because of a lack of substantial evidence of effectiveness.

The legality of marketing "me-toos" without an effective NDA was questionable, at least in the absence of a "not new drug" letter from FDA, because the criteria for an effective NDA in Section 505(b) also required applicants to show that their manufacturing processes were adequately controlled. A number of products were seized because this had not been shown by the manufacturer, even though there were effective applications for the same drug when manufactured by others.[17] However, the agency's ability to prevent such products from being marketed was limited. A major part of its professional staff was continuously engaged in reviewing for safety the voluminous NDAs filed in

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[16] Hearings before the Subcommittee on Public Health and Welfare, House Committee on Interstate and Foreign Commerce, on FDA Consumer Protection Activities—FDA Reorganization, 91st Cong., 1st and 2d Sess., at 230.

Altogether, there are estimated to be about 35,000 prescription drug products on the American market. See Hearings on Present Status of Competition in the Pharmaceutical Industry before the Subcommittee on Monopoly of the Senate Select Committee on Small Business, 92d Cong., 2d Sess., Part 22, at 8510.

[17] Annual Report of U.S. Department of Health, Education and Welfare (1959) at 207.

the decade prior to 1962,[18] which it received at an average rate of more than one per day. Moreover, the law did not require manufacturers and packagers of drugs to register their products with the agency, and no general census of products on the market existed.[19] The agency therefore could not effectively police the market for "me-too" products except by occasional, almost random proceedings. In some instances, where the product and its labeling appeared virtually identical with products for which NDAs had become effective under the Act's safety standard, the agency's staff issued opinions advising that the products would not be treated as "new drugs" under the Act.[20]

Finally, the agency was hampered by its inability to proceed against drugs which were therapeutically ineffective. In 1939 the head of the agency, in reporting on applications that had become effective, noted

[18] In 1939, NDAs were filed containing as many as 2,000 case reports from 100 doctors investigating the safety, if not the effectiveness, of new drugs. Admin. Reps. at 927–928. By 1970, NDAs contained up to 250 volumes of data. The average NDA is about 30 volumes—a stack of data 10 to 12 feet high. Hearings on FDA Consumer Protection Activities—FDA Reorganization before the Subcommittee on Public Health and Welfare, House Committee on Interstate and Foreign Commerce, 91st Cong., 1st and 2d Sess., at 58, 146. Some NDAs now contain as many as 400 volumes of data.

[19] Not until 1972 did Congress adopt a Drug Listing Act, 86 Stat. 559.

[20] Admin Reps. at 1415. There are no data to show the number of drugs for which the agency issued "not new drug" letters. It is fair to say, however, that several thousand were issued. Annual Reports of U.S. Department of Health, Education, and Welfare (1963) at 312, (1964) at 301. This policy was abandoned in 1968. See p. 21, *infra*.

that "in many instances it is questionable whether they possess the therapeutic properties claimed for them," [21] and the agency's misgivings on the subject were reiterated as it gained experience.[22] Only by complex proceedings for mislabeling was the agency, on occasion, able to stop sale of a few ineffective products. In some instances involving drugs which were offered for treatment of life-threatening diseases, it was also able to consider effectiveness in relation to safety.[23]

C. THE HARRIS-KEFAUVER "EFFICACY AMENDMENTS" OF 1962

1. Legislative history

From late 1959 until mid-1961, the Senate Subcommittee on Antitrust and Monopoly, Committee on the Judiciary, conducted a study of administered prices in the drug industry, S. Rep. 448, 87th Cong., 1st Sess.

[21] Admin. Reps. at 927.

[22] Annual Report of the Federal Security Agency, Food and Drug Administration (1950) at 12.

[23] In 1961, Secretary of Health, Education, and Welfare Ribicoff testified before Congress on the need for efficacy data in NDAs, stating: "It is important to recognize that evaluating effectiveness is not a new concept in the administration of the food and drug law. In some instances the decision as to safety of a new drug necessarily requires an evaluation of effectiveness. If the drug is offered for treatment of progressive or life threatening diseases, such as cancer, or if the drug is seriously toxic or has alarming side effects, we now consider its effectiveness. In such cases, the determination of safety is, in the light of the purpose of the new drug provisions, inseparable from consideration of the drug's effectiveness." Hearings before the Subcommittee on Antitrust and Monopoly, Senate Committee on the Judiciary, 87th Cong., 1st Sess., on Drug Industry AntiTrust Act, Part 5, at 2588.

This was followed by the introduction of legislation to amend the 1938 Act.

On July 19, 1962, the Committee reported out a bill (S. 1552, 87th Cong.) designed to "keep unfit drugs off the market * * * and speed their removal should they reach the market." [24] A proposed amendment to Section 505 (21 U.S.C. (1958 ed.) 355) authorized suspension of an NDA "upon a finding that there is a lack of substantial evidence * * * that [the drug] will have the effect claimed for it." [25] But the bill did not alter the definition of "new drug," which remained a drug not generally recognized as safe.

At about the same time, reports of the thalidomide drug disaster startled the country.[26] On August 4, 1962, President Kennedy sent to the Chairman of the Senate Committee on the Judiciary a series of proposed amendments to the pending bill. These were introduced and explained on the floor of the Senate by Senator Kefauver (108 Cong. Rec. 15692–15698). They included, among other things, a proposal for affirmative administrative approval of NDAs in place of the existing procedure permitting applications to become automatically effective after a fixed time unless rejected; redefinition of "new drug" to include effectiveness, as well as safety; and a standard which would give meaningful content to the existing bill's

[24] S. Rep. No. 1744, Part 1, 87th Cong., 2d Sess., at 8.

[25] *Id.* at 16.

[26] Thalidomide, a tranquilizer which was extensively used in Europe with labeling asserting safety in treatment of pregnant women, resulted in teratogenic impairment to thousands of infants. See *id.* at 40–42.

undefined criterion for "substantial evidence" of effectiveness.

Because of the President's proposals and nationwide concern over the thalidomide tragedy, the Senate committee met again "to give further special consideration to the adequacy of the present provisions of the Food and Drug Act" from a safety and efficiency standpoint. On August 21, 1962, it issued a second part to its report, setting forth a substitute version of S. 1552 which was designed to "insure the reliability of drugs." [27]

The Committee reported four important changes relevant to these cases. First, the bill provided that "no new drug could go on the market without affirmative approval by the Department." [28] Second, it added effectiveness to the safety standard in the definition of "new drug." The Committee explained that "[t]he effect of this change is to require that all claims for effectiveness, whether made initially in a new-drug application or at any time thereafter, must be supported by 'substantial evidence'" as defined in the amendments, and that this change was being made in order "to eliminate any possible ambiguity" on this point.[29]

Third, it specifically defined "substantial evidence" in terms of adequate and well-controlled studies by experts, as distinguished from anecdotal evidence

[27] S. Rep. No. 1744, Part 2, 87th Cong., 2d Sess., at 1.
[28] *Id.* at 4.
[29] *Id.* at 5.

by individual practitioners. The Committee explained that:[30]

> a claim could be rejected if it were found (a) that the investigations were not "adequate"; (b) that they were not "well controlled"; (c) that they had been conducted by experts not qualified to evaluate the effectiveness of the drug for which the application is made; or (d) that the conclusions drawn by such experts could not fairly and responsibly be derived from their investigations. * * *
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> * * * The question of whether the claim would or would not be allowed would be determined by [the Secretary's] evaluation of whether the claim had been supported by substantial evidence as defined above.

Fourth, the Committee proposed detailed transitional provisions, including a grandfather clause, for the new effectiveness standard. These provided that outstanding NDAs would be treated as approved under the new standard unless they were made the subject of further proceedings; that manufacturers would have a two-year grace period in which to gather substantial evidence of effectiveness; and that "in the case of a drug on the market which was never subject to the new-drug procedure before," the new effectiveness standard "would not apply to existing labeling claims."[31] Beyond making clear that drugs which had not been legally subject to the 1938 Act were not to be subject to the new amendments, there

[30] *Id.* at 6.
[31] *Id.* at 8.

was little other explanation of the grandfather provision.[32] Me-too drugs were not discussed during the debates when the bill passed the House and Senate. In conference, the Senate version of the grandfather provisions was adopted.[33] The bill finally enacted, save for certain additional amendments not here relevant, was substantially the revised bill proposed by the Senate Committee.

2. The Act as amended

For purposes of the present cases, the relevant substantive provisions of the 1962 Act (76 Stat. 780) are those dealing with efficacy and the definition of substantial evidence. As amended, Section 201(p)(1) now defines "new drug" as any drug not generally recognized among experts as safe *and effective* for its intended use. 21 U.S.C. 321(p)(1), J.A. 475. Section 505(a) bars the marketing of a new drug unless an approved application is in effect for it. 21 U.S.C. 355(a). Section 505(b) now requires an applicant to submit data demonstrating the safety *and efficacy* of the product involved. 21 U.S.C. 355(b), J.A. 477. The Secretary must either approve or disapprove the application within 180 days. Section 505(c), 21 U.S.C. 355(c). Section 505(d) requires the Secretary, after

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[32] Senator Eastland explained the Committee's revised bill on the floor of the Senate. Discussing the grandfather provision, he said: "Established drugs which have never been required to go through new drug procedures will not be affected by the new effectiveness test insofar as their existing claims are concerned." 108 Cong. Rec. 17366.

[33] H. Rep. 2526, 87th Cong., 2d Sess., at 22–23.

notice and opportunity for hearing, to refuse to approve the application if he finds a lack of "substantial evidence" of the product's efficacy. 21 U.S.C. 355(d), J.A. 478–479. Section 505(e)(3) now requires the Secretary to withdraw approval for an NDA, after notice and opportunity for hearing, if he finds upon the basis of new information a lack of "substantial evidence" of the drug's efficacy. 21 U.S.C. 355(e)(3), J.A. 479. Section 505(d) defines "substantial evidence" of effectiveness, as used in that subsection and in subsection (e), as "adequate and well-controlled investigations" from which qualified experts could conclude that the product is effective. Orders denying and withdrawing approvals are made directly reviewable in the courts of appeals. Section 505(h), 21 U.S.C. 355(h), J.A. 480–481.

Also relevant are the transitional and grandfather provisions. Since the Act was amended to require affirmative agency approval under the new standards, NDAs "effective" prior to the 1962 amendments were deemed "approved" under the new standards. This approval could not be withdrawn for lack of substantial evidence of effectiveness under Section 505(e)(3) for a period of two years. P.L. 87–781, 76 Stat. 788–789, Sections 107(c)(2) and 107(c)(3)(B), J.A. 481–482. The "grandfather" clause for the new efficacy provisions exempted any drug which, on the day preceding the enactment date (*i.e.,* October 9, 1962) was (A) sold in the United States, (B) generally recognized as safe, and (C) "not covered by an effective application under Section 505," so long

as its intended uses remained unchanged. P.L. 87-781, Section 107(c)(4), J.A. 482.

The injunctive, criminal, and seizure provisions of the 1938 Act remained essentially unchanged.

D. FDA'S IMPLEMENTATION OF THE 1962 AMENDMENTS

During the four years following enactment of the 1962 amendments, the agency concentrated on processing the large number of NDAs filed as a result of the new legislation. By 1966 the backlog was overcome, as the number of original NDAs received in that year dwindled to 147 [34] from a high in 1963 of 1,149.[35] The agency then took its first steps to review efficacy claims of drugs that had been cleared for marketing before 1962 on the basis of safety data only.

1. The NAS–NRC Drug Efficacy Study. To aid it in reviewing efficacy claims for every drug cleared for marketing before passage of the 1962 amendments, the FDA called upon the National Academy of Sciences-National Research Council (NAS-NRC).[36] This organization established a Drug Efficacy Study Group to determine whether there was appro-

[34] Annual Report of U.S. Department of Health, Education, and Welfare (1966), at 198.

[35] Annual Report of U.S. Department of Health, Education, and Welfare (1963), at 311.

[36] The National Academy of Sciences was created by Act of Congress in 1863 (12 Stat. 806). It is a non-governmental organization of scientists, whose duties include investigating and reporting upon scientific matters at the request of government departments. The NAS organized the National Research Council under its charter at President Wilson's request (see Executive Order 2859 (May 11, 1918), as amended by Executive Order 10668 (May 10, 1956), 21 Fed. Reg. 3155). The NRC is, in effect, the principal operating agency for the NAS.

priate scientific evidence to support the efficacy claims of those drugs. Thirty panels, each composed of six experts in a particular field of drug therapy, reviewed the manufacturer's claims and its evidence of efficacy for the drugs in their field of expertise (there were, for example, panels on drugs for relief of pain, anesthesiology, dermatology, ophthalmology, etc.).[37] To facilitate this review, manufacturers were ordered to submit to the appropriate panel or panels a special report containing the best available evidence in support of the efficacy claims for their drugs.[38] The report was to include identification of the drug, copies of its labeling, a bibliography of publications pertinent to the claims and any available unpublished data that the manufacturer wished to have considered. 31 Fed. Reg. 9426, 13014, J.A. 193–194, 288–289.

The panels based their conclusions upon factual information from scientific literature, from the Food and Drug Administration, and from the manufacturer or other sources, as well as upon the experience and informed judgment of the members of the panels.[39] Of the some 4,000 drug formulations still marketed by 237

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[37] Drug Efficacy Study: Final Report to the Commissioner of Food and Drugs, Food and Drug Administration, from the Division of Medical Sciences, National Research Council, National Academy of Sciences, Washington, D.C., 1969, at 1–3 (hereafter "NAS–NRC Report").

Ten copies of this Report have been furnished to the Clerk of this Court.

[38] Drugs involving claims falling within the scope of inquiry of more than one panel were reviewed by each panel with respect to the claim or aspect of a claim relevant to its inquiry. NAS–NRC Report, at 5.

[39] *Id.* at 42.

firms, the panels found a "considerable number" effective and about 7 percent ineffective or ineffective as fixed combinations for all claims; the majority received varying findings of "probably effective," "possibly effective," "effective but," and "effective" for some of the numerous claims made in each drug's labeling.[40] The Academy expressed concern over the quality of evidence available to support the efficacy claims of these drugs:[41]

> * * * Many of the presentations submitted by manufacturers in support of the claims made for the use of their drugs consisted of bulky files of reports of uncontrolled observations and testimonial-type endorsements. *The lack of substantial evidence based on well-controlled investigations by experienced investigators was conspicuous.* Moreover, searches of the medical literature indicated that there existed little convincing scientific evidence to support many of the cited indications for the use of drugs that are currently in good standing in medical practice. * * * [Emphasis added.]

Of some 16,500 claims made in the labeling of these drugs, only about 19 percent were found to be effective. The other claims, rated variously from "ineffective" to "effective but", were found not to be supported by substantial evidence of effectiveness.[42] Al-

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[40] *Id.* at 5, 7, 12.

[41] *Id.* at 13.

[42] See Hearings before the Subcommittee on Monopoly, Senate Select Committee on Small Business, 92d Cong., 1st Sess., on Present Status of Competition in the Pharmaceutical Industry, Part 20, at 7975. After allocation of "effective but" claims to other categories, about 30% of the claims were deemed effective (*id.* at 7976).

though the NAS–NRC panels reviewed more than 4,000 drugs for which NDAs were in effect, they did not specifically evaluate the still unknown larger number of me-too drugs.[43]

2. *Implementation of the NAS–NRC study.* On January 23, 1968, FDA held a government-industry conference and announced its policy of applying to all drugs, including "me-too" drugs, the applicable NAS–NRC efficacy findings.[44]

The agency believed that it would be inconsistent and unjust to drug manufacturers and to the public to construe the Act as requiring manufacturers of the "pioneer" drugs, who had filed an NDA, to produce substantial evidence of effectiveness or lose their marketing approval, while at the same time permitting "me-too" drugs, which owed their marketability to the pioneer NDAs, to remain on the market without demonstrating effectiveness. Construing the 1962 amendments as a mandate to assure that *all* pre-1962 drugs be shown effective as well as safe, the agency interpreted the words "covered by an effective application" in the 1962 grandfather clause (Section 107(c)(4)(C)) to refer "generically" to all of the types of drugs for

[43] Hearings before the Senate Committee on Labor and Public Welfare, on Drug Listing Act, 1971, 92d Cong., 1st Sess., at 21–22.

[44] *FDA Papers*, March 1968, at 15–16. This publication is the official magazine of the FDA, published monthly. It contains, *inter alia*, the notices of judgments, decrees, and court orders required to be published under Section 705 of the Act, 21 U.S.C. 375, as well as other information authorized to be published by that provision. Two copies of the March 1968 edition are being lodged with the Clerk of this Court.

which at least one NDA had become effective. Its interpretation precluded "grandfather" protection for all pre-1962 drugs identical, similar or related to those for which an NDA was permitted to become effective. Accordingly, participants at the January 1968 conference were told that the NAS–NRC findings would be applied not only to "drugs which were specifically the subject of prior new-drug approvals but also any 'me-too' drugs * * *." [45]

The participants were also advised that the very first notice proposing withdrawal proceedings to implement the NAS–NRC findings (covering bioflavonoid products [46]) would be a model for future actions insofar as it would "classify all drugs containing any [ineffective] components as new drugs for which an approval is not in effect." [47]

Plans to classify those drugs generally recognized as safe and effective for labeled indications were also disclosed at that conference,[48] as well as the agency's policy to require manufacturers to file either full, abbreviated, or supplemental NDAs for changes in labeling or drug composition determined to be necessary by the NAS–NRC findings.[49]

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[45] *Ibid.*

[46] 33 Fed. Reg. 818 (J.A. 290). These are the products involved in *USV Pharmaceutical* (No. 72–666).

[47] *FDA Papers*, March 1968, at 16.

[48] *Id.* at 10.

[49] *Id.* at 11. A complete NDA is required for an unapproved "new drug." 21 C.F.R. 130.4. Supplemental applications are required for a change in either the labeling or composition of an NDA'd drug. 21 C.F.R. 130.9. In the case of a "new drug"

On May 28, 1968, the agency, by formal statement of policy premised on the need for full implementation of the NAS–NRC findings, revoked all opinions previously given to the effect that an article is "no longer a new drug."[50] On July 10, 1968, the first notice of opportunity for hearing on a proposal to withdraw NDA approvals was published.[51] Other proposals followed, and approximately 600 have been issued to date.

FDA has recently adopted a regulation declaring the manner in which Drug Efficacy Study Implementation ("DESI") Notices and Notices of Opportunity for Hearing apply to identical, related, and similar drugs. It defines an "identical, related, or similar drug" to include "other brands, potencies, dosage forms, salts, and esters of the same drug moiety as well as of any drug moiety related in chemical structure or known pharmacological properties."[52] It also provides all persons with an interest in such drugs an opportunity for hearing on any proposed withdrawal of NDA approval for the basic drug.[53]

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shown in connection with a previous NDA approval to be safe and effective, a manufacturer of the same or a similar drug not having an NDA may file an abbreviated application containing the information required by 21 U.S.C. 355(b), except safety and efficacy data. In certain instances, therapeutic equivalency must be demonstrated. 21 C.F.R. 130.4(f).

[50] 33 Fed. Reg. 7758; 21 C.F.R. 130.39 (J.A. 291–292).

[51] 33 Fed. Reg. 9908 (J.A. 293).

[52] 37 Fed. Reg. 23185, adding Section 130.40 to 21 C.F.R.

[53] In *American Public Health Association* v. *Veneman*, Civil No. 1847–70 (D.D.C.), a district court ordered the agency to

3. *Regulations defining "adequate and well-controlled investigations" and requiring proffer of evidence conforming to that definition as a basis for hearing.* As a result of the NAS–NRC study and its implementation by notices proposing to withdraw approvals on drugs found to be lacking substantial evidence of effectiveness, the agency was faced with the prospect of more than 1,000 withdrawal hearings under Section 505(e), each lasting several months.[54] This would have delayed for many years achievement of the purposes of the 1962 amendments. The agency therefore issued regulations in 1969 defining the "scientific principles which characterize an adequate and well-controlled clinical investigation,"[55] the standard for "substantial evidence" in Section 505. The rule also provided that, unless a party seeking a hearing was prepared to proffer such evidence, no basis for a hearing was presented.[56] Following re-promulgation of these regulations in May 1970 to comply with the rule-making provisions of the Administrative Pro-

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apply the NAS–NRC evaluation to all me-too drugs (see paragraph XI of the order). The order is reproduced at 37 Fed. Reg. 26623–26624.

[54] Of the drugs reviewed by NAS–NRC, more than 3,500 made one or more claims not rated effective, and withdrawal of approval is in prospect for most of these claims. In many instances, however, several products contain similar drugs, so that consideration of withdrawal of approval for similar claims can be undertaken with respect to several products in a single, consolidated proceeding. Thus, the precise number of such proceedings is impossible to estimate.

[55] 34 Fed. Reg. 14596.

[56] *Id.*

cedure Act,[57] they were sustained on judicial review.[58]

4. The Drug Listing Act of 1972. By May 1972, 102 final orders effecting withdrawal of approval for 452 NDAs had been published. These orders also resulted in removal from the market of an additional 1,473 related or "me-too" drugs.[59] However, FDA still had no assurance that its implementation efforts were broadly effective, for a census of the marketplace was not authorized by the statute.

On August 16, 1972, in an effort to provide the agency with the tools necessary to effectuate the findings of the NAS–NRC review, Congress enacted the Drug Listing Act of 1972, P.L. 92–387, 86 Stat. 559. It requires manufacturers to submit to the agency a list of all drug products they market, including data showing the composition of the drugs, their labeling and advertising. The Senate report explained the necessity for this legislation.[60]

> The effective enforcement of the drug provisions of the Act requires the ready availability of a current inventory of all marketed drugs.

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[57] 35 Fed. Reg. 3073; 35 Fed. Reg. 7250. The regulations had been set aside in *Pharmaceutical Manufacturers Association* v. *Finch*, 307 F. Supp. 858 (D. Del.), for failure to give the public an opportunity to comment upon them. In a suit by a manufacturer which had actual notice of the procedures, however, a court of appeals held that the agency's definition of "substantial evidence" complied with the intent of Congress. *Upjohn Co.* v. *Finch*, 422 F. 2d 944 (C.A. 6).

[58] *Pharmaceutical Manufacturers Association* v. *Richardson*, 318 F. Supp. 301 (D. Del.).

[59] Hearings on the Present Status of Competition in the Pharmaceutical Industry before the Subcommittee on Monopoly of the Senate Select Committee on Small Business, 92d Cong., 2d Sess., Part 22, at 8525.

[60] S. Rep. No. 92–924, 92d Cong., 2d Sess., at 2.

> The Secretary is just completing a thorough review of the effectiveness of drugs marketed pursuant to new drug applications during the period 1938–1962, as required by the Drug Amendments of 1962. Application of the results of this important review to related drugs would be frustrated if a list of all marketed drugs were not easily obtained. * * *

The first filing of the drug lists by the industry will take place during June 1973. 37 Fed. Reg. 26432.

5. Regulations Pertaining to Over-the-Counter Drugs. FDA has also recently concluded that it is impossible for it to apply the Drug Amendments of 1962 effectively to over-the-counter (OTC) drugs on a case-by-case basis. There are estimated to be between 100,000 and 500,000 of these products, few of which were previously approved under the Act and many of which are of questionable efficacy. FDA does not have the resources to proceed against these products individually, and the time consumed by litigation would deny the public protection for many years to come. 37 Fed. Reg. 85–86. It therefore proposed (*id.*) and, in May 1972, adopted (37 Fed. Reg. 9464) a procedure for determining in substantive rule making, by therapeutic class, whether particular OTC products not covered by NDAs are generally recognized as safe and effective and not misbranded, under the standards of the Act. The procedure involves the establishment of independent expert panels for different categories of OTC drugs (*e.g.*, antacids, laxatives, analgesics), which would review all available data (including any that manufacturers, consumer groups, or others wish to submit) and prepare monographs prescribing drug

composition, labeling, and manufacturing controls. Products conforming to the monograph-rule will not be considered to be "new drugs" requiring an NDA or to be misbranded. The regulation contemplates substantial procedural safeguards at the administrative level (a hearing before the expert panel, comments and rebuttal comments on the proposed monograph-rule, and objections to and hearing before the Commissioner on the tentative final monograph-rule) and judicial review of the monograph-rule, which could thereafter be enforced in the courts as binding (37 Fed. Reg. 9464, 9475).

II. THE FIVE CASES CONSOLIDATED IN THIS COURT

The five consolidated cases relate to numerous important aspects, both substantive and procedural, of FDA's efforts to accomplish the purposes of the 1962 efficacy amendments as applied to drugs that came on the market prior to 1962. *USV Pharmaceutical* (No. 72–666) and the cross-petition in *Hynson, Westcott and Dunning* (No. 72–414) pose questions as to which classes of drugs marketed prior to 1962 are subject to the Act's requirement of proof of efficacy for continued marketing. They involve principally the construction of the transitional and grandfather provisions of Section 107(c). The government's petition in *Hynson, Westcott and Dunning* (No. 72–394) concerns the validity and application of FDA's procedural regulations requiring a manufacturer of a drug to support its request for an evidentiary hearing in a withdrawal proceeding with a showing that it can adduce the kind of evidence required by statute to establish the efficacy

of the drug. *CIBA* (No. 72–528), the cross-petition in *Hynson, Westcott and Dunning* (No. 72–414), and the present case raise the question, in varying contexts, whether FDA has authority to decide initially in an administrative proceeding whether a product is subject to the proof-of-efficacy provisions of the Act. In *CIBA* and *Hynson, Westcott and Dunning* the question arises in the context of an agency proceeding to withdraw marketing approval previously obtained by the manufacturer. In the present case, the question is whether FDA may decide that issue pursuant to a referral from a district court.

III. THE INSTANT CASE

Administrative Proceedings. Prior to 1962, under the safety standard of the 1938 Act, FDA had permitted NDAs covering pentylenetetrazol combination drugs [61] to become effective. The NDAs were held by firms not involved in the present case. As part of the comprehensive DESI program (see pp. 19–21, *supra*), three separate NAS–NRC panels reviewed the available evidence concerning these drugs (J.A. 235–247).[62] Each panel concluded that the drug was "ineffective"

[61] These are prescription drugs offered for senile psychosis and psychoneurosis, with anxiety and nervous tension, senile fatigue, confusion, debilitation, depression, dizzy spells, mild behavioral disorders, irritability and functional memory defects (J.A. 233).

[62] The specific drugs evaluated were NICOZOL with RESERPINE (a combination of pentylenetetrazol, nicotinic acid and reserpine) and GERONIAZOL injection (a combination of pentylenetetrazol and nicotinic acid administered by injection) (J.A. 235, 240–241).

for each of its indicated uses (J.A. 237, 239, 244, 245, 247).

After evaluating the NAS–NRC reports on drug combinations containing pentylenetetrazol, the Commissioner concluded that there was a lack of substantial evidence that these drugs are effective for their intended uses. On August 26, 1969, he published a notice (34 Fed. Reg. 13673, J.A. 226–228) setting forth his conclusion and announcing his intention to initiate proceedings to withdraw approval of the NDAs for these drugs. The notice invited the holders of the NDAs "and any interested person who might be adversely affected by [the drugs'] removal from the market" to submit any "adequate and well-controlled studies bearing on the efficacy of" the drugs in question. The notice reflected FDA's view that withdrawal of approval of the NDAs would operate to remove marketing approval not only for the particular drugs expressly covered by the NDAs, but also for any drugs of similar composition. It stated that an order withdrawing approval of the NDAs "will cause any such drug on the market to be a new drug for which an approved new-drug application is not in effect and will make it subject to regulatory action."

Only one firm, a holder of one of the three NDAs outstanding, submitted further material in response to the notice. On May 20, 1970, the Commissioner announced that substantial evidence of effectiveness within the meaning of the statute (21 U.S.C. 355(d)), was lacking and that he therefore proposed to issue an order under Section 505(e) of the Act (21 U.S.C. 355

(e)) withdrawing approval of the NDAs. The three firms that held approved NDAs "and any interested person who would be adversely affected" by such action were again offered an opportunity for a hearing. The agency also again declared that withdrawal of approval for the NDAs would cause any drug containing the same substances to be a "new drug" for which an approved NDA is not in effect (35 Fed. Reg. 7749, J.A. 228–230). Only one NDA holder requested a hearing, but it filed no data to support its request. Accordingly, the Commissioner issued orders withdrawing approval for the three NDAs then in effect (35 Fed. Reg. 14412, J.A. 231, 232). No appeal was taken to review this action.

The NAS–NRC efficacy review of drugs containing pentylenetetrazol and the ensuing agency proceedings that culminated in the order withdrawing approval of the NDAs would have offered little protection to the public if others continued to market identical or substantially similar drugs ("me-too" drugs). Accordingly, the agency issued advisory letters to various firms intended to effect the removal from the market of all "me-too" drugs containing pentylenetetrazol. For example, on November 4, 1970, FDA wrote Bentex Pharmaceuticals advising it of FDA's action withdrawing approval for NDAs on drugs similar to Bentex products containing pentylenetetrazol and stating that, in view of this, those Bentex products were no longer marketable (J.A. 254, n. 3).

The Decision of the District Court. On December 1, 1970, Bentex and 22 other firms [43] that market drugs containing pentylenetetrazol filed this suit for declaratory and injunctive relief (J.A. 219–226). They contended that their drugs containing pentylenetetrazol either (1) are not "new drugs" within the meaning of Section 201(p)(1) of the amended Act (21 USC 321(p)(1)) (*i.e.*, that they are currently generally recognized as safe and effective) or (2) are exempted by the grandfather clause from the requirements of the amended Act (J.A. 223).[44] They accordingly sought a ruling declaring invalid and unenforceable the Commissioner's position that their drugs are "new drugs" for which no NDA is in effect and which therefore cannot legally be marketed.

The district court held that the declaratory judgment action was properly before it and that it could determine whether plaintiffs' drugs required approved NDAs in order to be lawfully marketed—*i.e.*, whether or not they are "new drugs" or "grandfathered" drugs (J.A. 256). It thus rejected the government's conten-

[43] A twenty-fourth firm, O'Neal, Jones & Feldman, Inc., which alleged that it contemplated the sale of drugs containing pentylenetetrazol (J.A. 220), was stricken as a plaintiff in this case at its request.

[44] The complaint asserted that the drugs involved were protected by the grandfather clause of the 1938 Act, set forth in Section 201(p)(1), which applies to drugs marketed before 1938 (J.A. 223). It later became clear that plaintiffs were actually relying on the grandfather provision in Section 107(c)(4) of the 1962 amendments.

tion that FDA has primary and exclusive jurisdiction to determine that issue (J.A. 255). But the district court also rejected the argument, advanced by plaintiffs, that the status of their drugs could be determined only by the district court. It ruled that the statutory "grant of authority to approve or withhold approval of new drug application [*sic*], or to proceed with regulatory action in the courts, necessarily implies authority for F.D.A. to determine the threshold question of whether the article involved is a drug which requires an approved new drug application for lawful interstate shipment" (*ibid.*).

Having found concurrent jurisdiction, the district court concluded that FDA, as "the more able arbiter of the question," should resolve the "new drug" issue in an administrative proceeding in which plaintiffs and other interested parties could participate (J.A. 256).[65] The court entered an injunction to preserve the *status quo*, barring enforcement proceedings against the drugs involved pending resolution by FDA of the question whether they require approved NDAs in order to be lawfully marketed. If the agency should decline to hold a hearing and decide the issue, the court stated it would then determine the issue itself (J.A. 257–258).

The Decision of the Court of Appeals. On appeal by the plaintiff drug manufacturers,[66] the court of

[65] The district court stated that an appeal from FDA's determination would lie to the court of appeals (J.A. 256). We believe, however, that FDA's determination in response to the court's referral order would be reviewable in the district court. See *infra*, pp. 52–53.

[66] The government did not appeal.

appeals reversed and remanded the case to the district court with directions that it determine whether plaintiffs' drugs may lawfully be marketed without approved NDAs (J.A. 258–270).[67]

The court of appeals held that the Act confers no jurisdiction on FDA, either primary or concurrent, to decide in an administrative proceeding whether a product is a "new drug" for which an NDA is required. There is thus no basis, it concluded, for referring the issue to the agency, because the agency has no authority to decide it (J.A. 266). The court based this conclusion on its construction of the Act as "establish[ing] two forums for the regulation of drugs: One is administrative and deals with the procedures for securing pre-marketing clearances for the statutorily defined 'new drug', with right of appeal from a denial of approval, or withdrawal of a previous approval * * *; the other is judicial and is intended to make effective and give strength to the requirement that 'new drugs' be cleared as safe [and, after 1962, effective] before marketing by providing the Government with certain potent judicial remedies [seizure, injunction and criminal prosecution], *available exclu-*

[67] The court of appeals expressed the view that the only substantive issue in the case is whether respondents' drugs are exempt from the proof of efficacy requirement of the amended Act by reason of the grandfather provision, Section 107(c)(4), and it directed the district court to determine that issue on remand (see J.A. 263, 269). So far as we are aware, however, respondents have not abandoned their claim that their drugs are not "new drugs" within the meaning of Section 201(p)(1), *i.e.*, that they are now generally recognized as safe and effective.

sively in the District Court" (J.A. 260; emphasis in original).

The court stated that since there is no express provision in the Act for an administrative determination of whether a particular drug is a "new drug" requiring an NDA, and no provision for judicial review of such a determination (J.A. 259, 267–268), the manufacturer, "who must act at its peril," must decide whether an NDA is required for the lawful marketing of a particular drug (J.A. 260, 268). In the court of appeals' view, the correctness of the manufacturer's determination must be decided exclusively by the district court, either in an action initiated by the government or in an anticipatory declaratory judgment action like this one, if the agency has made known its "prosecutorial" views (J.A. 266–267, 269).

The court of appeals expressly rejected the district court's reasoning that the statutory grant of authority to FDA to approve or withhold approval of NDAs necessarily implies authority to resolve the threshold question whether an approved NDA is required. "No such issue," the court of appeals said, "is posed by the application" (J.A. 268). Rather, the filing of the application represents a "concession" by the manufacturer that its drug is a "new drug" requiring administrative approval. The sole question raised by an application is whether the drug is safe and effective, and the agency may determine only that issue when an application is filed (*ibid.*). The court held that if the manufacturer chooses not to make that concession, but rather to market at its peril, the courts provide

the only forum within which the legality of that choice may be determined.

The court of appeals remanded the case to the district court for determination of the substantive issues involved (J.A. 269–270).

ARGUMENT

INTRODUCTION AND SUMMARY

The court of appeals has ruled that FDA lacks power, in all circumstances, to determine whether particular drugs require an approved NDA in order to be sold to the public.[68] Although Congress assigned the agency primary responsibility for determining whether drugs proposed for sale, or now being sold, are safe and effective for their intended use, the decision below nevertheless holds that FDA cannot determine the threshold question whether particular products are "new drugs" subject to its jurisdiction under Section 201(p) of the Act. It follows, under this rea-

[68] That the court below considered its ruling to bar administrative determination of the Act's coverage in any circumstances is demonstrated by its rulings in two of the related cases pending in this Court. In *Hynson, Westcott and Dunning*, No. 72–394, a petition for review of the agency's order withdrawing NDAs, the court held that a manufacturer is entitled to have the district court resolve its claim for exemption, under the grandfather clause of the 1962 amendments, from the new efficacy requirements (J.A. 176–177). And in *USV Pharmaceutical*, No. 72–666, an appeal by the government from a district court judgment declaring a manufacturer's products exempt under the grandfather clause, the court of appeals, citing its decision in the instant case, ruled that the district court alone had jurisdiction to determine these questions (J.A. 467).

soning, that it cannot determine whether such products are exempted from the efficacy requirements of the Drug Amendments Act of 1962 by the grandfather clause in Section 107(c)(4) of that Act. If the court of appeals is correct, only the courts may make these determinations, even though the agency's jurisdiction depends on them.

This decision strikes at the heart of the statutory scheme for administrative examination of drugs for safety and effectiveness. That scheme contemplates that before drugs are marketed they will be examined by an expert agency in the light of the best scientific information available, and that they will thereafter be reexamined in the light of developing knowledge whenever this is necessary to protect the public. But the decision below would, in all instances, effectively transfer to the courts resolution of the complex medical and pharmacological questions upon which the definition of "new drug" turns. An enormous volume of case-by-case litigation would thus be thrust upon district courts, whose dockets are already crowded. Moreover, the courts are not equipped with expert scientific staffs to investigate and resolve the technical questions presented, nor do they have the broad range of administrative powers, including rule-making, by which the agency can create procedures to reduce to manageable proportions the enormous numbers of products and claims which must be examined. See, *e.g., Abbott Laboratories* v. *Gardner,* 387 U.S. 136, 147, 149–150, 151–152; *Securities and Exchange Commission* v. *Chenery Corp.,* 332 U.S. 194, 202; *Ciba-Geigy Corporation* v. *Richardson,* 446 F. 2d 466, 467-

468 (C.A. 2); *American Airlines, Inc.* v. *Civil Aeronautics Board*, 359 F. 2d 624, 629–630 (C.A.D.C.), certiorari denied, 385 U.S. 843.

The holding of the court of appeals is directly inconsistent with the established principle that administrative agencies having regulatory responsibilities with respect to particular industries, in the absence of conflict with other statutory schemes,[69] have primary authority to determine the coverage of the Act they administer. It is also inconsistent with principles governing the discretion of district courts in declaratory judgment actions. And it threatens virtually to paralyze achievement of the basic objective of the 1962 amendments—removal from the market of *all* unsafe and ineffective drugs.

As a practical matter, the agency cannot proceed entirely on a case-by-case, drug-by-drug, and claim-by-claim basis against every drug currently marketed or to be marketed that does not meet the standards of the 1962 amendments. Nor, we submit, are the federal courts equipped to handle a flood of complex scientific litigation. Under the court of appeals' rationale, however, in every instance in which an NDA is withdrawn by the agency after full administrative proceedings, and even after that decision is sustained in the court of appeals on petition for review, the manufacturer would have the right to litigate afresh in a district court the question whether the drug involved required an NDA in the first place.

[69] Cf. *Ricci* v. *Chicago Mercantile Exchange*, No. 71–858, decided January 9, 1973.

Moreover, the decision invites manufacturers of "me-too" drugs to refrain from participating in agency proceedings for the withdrawal of approval for the primary NDA, in order to litigate in the district courts the question whether their drugs require approved NDAs to remain on the market. The court below thus encourages, indeed mandates, a two-step proceeding: first, a full scale administrative proceeding denying or withdrawing approval under Section 505; then a separate series of judicial proceedings to establish whether the Act's requirements should be applied at all. If permitted to stand, the court of appeals' holding therefore would, at a minimum, inordinately protract FDA's efforts to discharge its congressionally assigned responsibility to remove from the market drugs not shown to be effective.

By contrast, the district court's decision, referring issues of the Act's coverage to the agency responsible for administering it, would encourage manufacturers, whether producers of NDA's or "me-too" drugs, to look to FDA in the first instance to determine the applicability of the Act to their products.[70]

Moreover, the implications of the decision below extend beyond the area of prescription drugs involved

[70] In the government's view, a drug found to be a "me-too" drug would have been "covered by" an effective NDA at the time of the 1962 amendments and would therefore not be within the grandfather provision of Section 107(c)(4). This issue is involved in *USV Pharmaceutical* (No. 72-666). If FDA's position is sustained, the "me-too" manufacturers will have a compelling incentive to participate in proceedings to determine whether approval of the primary NDA should be withdrawn for lack of efficacy of the drug involved.

in the present case. The agency's current program to review the over-the-counter drugs (see pp. 24–25, *supra*) would also be undermined by the court of appeals' rationale, since the agency would have no power to determine definitively, subject to judicial review, standards by which hundreds of thousands of drugs for which no NDA is in effect may be classified as "new drugs" or not. The agency would be required to pursue these products throughout the courts of the Nation in innumerable trials considering *de novo* issues that are best suited to administrative resolution and that may, indeed, already have been given careful consideration in administrative proceedings. The decision of the court of appeals would thus leave the agency virtually impotent to deal effectively with the vast task of implementing the 1962 amendments.[71]

Nothing in the Act requires results so crippling to its effective implementation. Congress assigned to the agency a responsibility affecting the lives and health of all Americans—to assure that drugs sold in the United States are safe and effective. This responsibility carries with it the grant of a commensurately wide range of express and implicit powers neces-

[71] The implications of the decision below extend beyond drugs and would apparently also affect the agency's authority to determine administratively whether food ingredients are generally recognized as safe under 21 U.S.C. 348 (see 37 Fed. Reg. 25705) or are grandfathered under 21 U.S.C. 321(s)(4) (see 37 Fed. Reg. 16407), to determine whether biologic substances licensed under 42 U.S.C. 262 are generally recognized as safe and effective (see 38 Fed. Reg. 4319), and to determine whether *in vitro* diagnostic products are safe and effective (see 37 Fed. Reg. 16613).

sary for achievement of the Act's ultimate purposes. Fundamental among these is the power to decide the threshold questions on which the agency's jurisdiction turns. This is clear from the structure of the Act itself, which places primary reliance on administrative pre-marketing clearance as the means of assuring that drugs sold to the American public are safe and effective for their recommended uses. The judicial remedies of injunction, condemnation, and criminal sanctions serve as a second line of defense, principally intended to channel maufacturers to the agency in the first instance.

The decision of the court of appeals that FDA has no jurisdiction to determine whether a product or class of products is a "new drug" requiring administrative pre-marketing clearance is rooted in several erroneous premises. Thus, contrary to the court's belief, there are procedural avenues available for consideration of the question by the agency, either in connection with the statutory proceeding for approval or withdrawal of an NDA (as in the companion *CIBA* case), or, if no NDA exists or is being sought, in a declaratory order proceeding pursuant to the Administrative Procedure Act. In either case, contrary to the assumption of the court below, judicial review of the agency's determination would be available—in the former instance, in the court of appeals by means of the Act's judicial review provision for actions affecting NDAs; in the latter, in the district courts pursuant to 28 U.S.C. 1331 and 1337 and the Administra-

tive Procedure Act's general provisions concerning review of final agency actions.

Finally, the court of appeals' assumption that there is a significant difference between the inquiry presented by the question of "new drug" status and that involved in the agency's review of NDAs for safety and efficacy is mistaken. Both inquiries focus upon expert evaluation of complex scientific data, and the substantial overlap in the content of the inquiries reinforces the conclusion that both were intended to be committed, wherever feasible, to the expert agency established by Congress to pass upon drug safety and efficacy.

Once the agency's jurisdiction to pass upon the questions referred to it by the district court in this case is recognized, the wisdom of the referral is apparent. The factual questions presented in this case—whether respondents' products are sufficiently similar to those for which NDAs were withdrawn for inefficacy to be "covered" by those NDAs; whether there exists substantial evidence of the effectiveness of respondents' products or general recognition, at any relevant time, of their safety or efficacy—turn upon the state of expert scientific opinion and upon complex chemical and pharmacological matters. Such matters are far better suited to initial determination by FDA rather than by a district court, and the referral to the agency in the instant case represented a sound exercise of the extensive equitable discretion vested in the courts in declaratory judgment proceedings.

I. FDA HAS AUTHORITY TO DECIDE WHETHER PARTICULAR DRUGS REQUIRE AN APPROVED NDA

A. THE SCHEME OF THE ACT CONTEMPLATES THAT AN EXPERT AGENCY WILL RESOLVE THE MEDICAL, CHEMICAL AND PHARMACOLOGICAL ISSUES INVOLVED IN DETERMINING "NEW DRUG" STATUS.

In concluding that the district court could not refer to FDA the question whether respondents' products are "new drugs" which require an NDA, the court of appeals held that the agency may never decide that question in its administrative capacity but may consider it only for the limited purpose of initiating enforcement proceedings in the courts. This holding, in our view, is based on an unduly narrow and mechanical reading of Section 505 of the Act which ignores the remedial purposes of the 1962 amendments and the over-all context of the Act, including the availability of proceedings authorized by the Administrative Procedure Act (see pp. 49–50, *infra*). It also misconceives FDA's administrative and prosecutorial functions. The former are intended to protect the public by providing pre-marketing administrative clearance and continuing post-marketing review for drugs in commerce. The latter, operating as a second line of defense, complement the agency's administrative functions by invoking judicial sanctions against those who fail to comply with the Act's regulatory requirements. This structure is apparent on the face of the Act.

1. The administrative provisions are the primary public safeguard. Section 505(a) of the Act (J.A. 477) expressly forbids introduction into commerce of "any

new drug, unless an approval of an application filed pursuant to subsection (b) of this section is effective with respect to such drug." Subsection (b) sets forth the requirements for filing an application with the Secretary of Health, Education and Welfare (*i.e.*, the Food and Drug Administration), and subsections (c) and (d) describe conditions for approval, with or without hearing, and grounds on which the agency may refuse an application. Subsection (d) includes the definition of "substantial evidence," which the manufacturer must present to support claims of the drug's effectiveness: "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have * * *" (J.A. 478). This is followed by subsection (e), which, recognizing that new research and clinical experience constantly change medical standards, contemplates that the agency will maintain a continuous surveillance of all previous approvals. Thus, the agency may withdraw previous approvals on the basis of new evidence that a product is unsafe or new information indicating that there is "a lack of substantial evidence" that the drug is effective (J.A. 479).

The statute thus contemplates a sweeping and comprehensive administrative responsibility, of a continuing nature, (1) to protect the public by screening

any "new drug" for safety and effectiveness prior to marketing, and (2) to maintain continuing surveillance of "new drugs" on the market in order to assure, in the light of developing medical knowledge and experience, that they are safe and effective for their intended use.

The broad powers of the agency to grant, refuse, or withdraw approvals are implemented by similarly broad powers to conduct hearings after due notice to the applicant (Section 505(c)(2), J.A. 477–478), "to promulgate regulations for the efficient enforcement of this Act" (Section 701(a), 21 U.S.C. 371(a)) and "to conduct examinations and investigations for the purposes of this Act" (Section 702(a), 21 U.S.C. 372 (a)).[12] Finally, any order of the agency refusing or withdrawing approval of an application may be appealed directly to the courts of appeals for review on the administrative record (Section 505(h), J.A. 480–481), so that the agency's exercise of its broad responsibilities is subject to the limited but important judicial scrutiny characteristic of American administrative law.

Congress has thus assigned the agency great responsibilities for the public health and conferred on it the full range of administrative powers to carry out these responsibilities: investigation, rule-making and administrative adjudication. There is every reason to construe this broad authority as including the power to decide the threshold question on which the agency's

[12] These powers, of course, extend beyond the drug provisions of the Act to the agency's responsibility for food, cosmetics, and other matters as well.

regulatory responsibility turns: Is the product involved a "new drug" for which approval is necessary under Section 505(a)?

"New drug" is a jurisdictional term of art in the statute. It is defined in Section 201(p) (J.A. 475) as "[a]ny drug * * * the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof * * *." The very statement of this definition, which must also be read in *pari materia* with the definition of substantial evidence in Section 505(d),[73] suggests a determination of technical and scientific questions by experts. It is thus an example of the classic administrative function—the resolution of technical issues of fact, requiring highly specialized knowledge, training and experience of a kind not ordinarily possessed by judges. See *Ricci* v. *Chicago Mercantile Exchange, supra; United States* v. *Western Pacific R. Co.*, 352 U.S. 59, 64–65, 65–66; *Far East Conference* v. *United States*, 342 U.S. 570, 574–575.

2. *The enforcement provisions complement the regulatory requirements.* When the enforcement provisions of the Act are read in relation to its regulatory provisions, it plainly appears that judicial proceedings are intended to complement, not displace, the regu-

[73] See S. Rep. 1744, Part 2, 87th Cong., 2d Sess., pp. 1, 5. See p. 41, *supra*.

latory scheme. The statute expressly lists, among other prohibited conduct, the introduction into commerce of any article in violation of Section 505's requirement of an NDA approved by the agency after administrative consideration. Section 301(d), J.A. 475. It prescribes civil injunction proceedings, criminal penalties, and *in rem* seizure and condemnation, to give effect to this as well as other prohibitions. Sections 302(a), 303, 304 (J.A. 475–477). The administrative system of pre-marketing clearance and continuing review is thus established by the Act as the primary means of safeguarding the public health from unsafe and ineffective drugs, while judicial sanctions reinforce the administrative agency as a second line of defense, hopefully functioning primarily to direct manufacturers to the agency in the first instance.

The court of appeals' decision, however, seriously departs from this system of administrative clearance supported by judicial review and sanctions. It would make the courts, not the agency, the principal forum for determining whether products are "new drugs" subject to the requirement of administrative clearance and review. Given the scientific and technical nature of the questions involved in these determinations, this would be an unusual policy choice for Congress, and, we submit, the language and structure of the Act do not require this unfortunate and impractical result.

The court of appeals considered it highly significant that there is "no provision in the Act for an administrative proceeding before the Secretary to compel the

filing of a 'new drug' application or to halt the marketing of a drug for which there is no approval by the Secretary" (J.A. 266). But this does not mean that, in the proceedings it does conduct, the agency is without power to determine its own jurisdiction. Sections 301 (d) and 505(a) together impose on manufacturers a duty to assure that their "new drugs" are covered by an approved NDA. The absence of administrative power to enforce this duty directly does not negate the agency's authority to make determinations with respect thereto. This Court so held in *Abbott Laboratories* v. *Gardner*, 387 U.S. 136, 151–152, where it rejected the government's argument that FDA's lack of administrative authority to enforce its regulations distinguished it from agencies having such power. Such administrative authority may be a useful remedial supplement to the judicial sanction, but it does not define the agency's substantive powers to resolve properly presented jurisdictional questions turning on technical matters peculiarly within the agency's competence.

Nor is it significant that in an enforcement proceeding the courts may determine for themselves whether a product is a "new drug," at least when the agency has not previously done so by formal administrative action.[14] For enforcement proceedings, which

[14] Where the agency has determined a question in formal administrative proceedings, subject to judicial review, a party to those proceedings may not, in the ordinary course, collaterally challenge that determination as a defense to an enforcement proceeding. See, *e.g.*, *United States* v. *Ruzicka*, 329 U.S. 287; *Yakus* v. *United States*, 321 U.S. 414, 444–446. This is

are brought in the name of the United States, are simply the last resort—the threat of judicial sanctions against those who disregard the administrative process. Such sanctions against operations without a permit required by statute are a familiar feature of the administrative process.[75] Indeed, even in an enforcement proceeding brought by the United States under a regulatory statute, technical questions under the statute within the primary jurisdiction of an agency may be referred to it. For example, in *United States* v. *Pacific & Arctic Navigation Co.*, 228 U.S. 87, a prosecution to enforce the antitrust laws and the Interstate Commerce Act, claims under the latter statute were referred to the Interstate Commerce Commission.[76] Similarly, under the scheme of the present Act,

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merely an application of the principle of collateral estoppel to interrelated administrative and judicial proceedings. Cf. *United States* v. *Utah Constr. Co.*, 384 U.S. 394, 422; *Marine Terminal Assn.* v. *Rederi. Transatlantic*, 400 U.S. 62, 72. See also 5 U.S.C. 703.

[75] See, *e.g.*, Sections 206(a) and 222(a) and (b) of the Motor Carrier Act, 49 U.S.C. 306(a), 322(a) and (b); Sections 401 and 902 of the Federal Aviation Act, 49 U.S.C. 1371 and 1472; Sections 301 and 501 of the Communications Act of 1934, 47 U.S.C. 301 and 501.

[76] In the present case, the government argued in the district court that FDA had primary jurisdiction and that the declaratory judgment action should be dismissed. Cf. *Far East Conference* v. *United States*, 342 U.S. 570, 576–577. But after the district court had ruled that it had concurrent jurisdiction, thereby rejecting the primary jurisdiction contention, it nevertheless referred the "new drug" question to the agency in the exercise of its equitable discretion. For purposes of this case, the government acquiesced in that determination and did not raise the primary jurisdiction argument on appeal. Consequently, it is not presented in this Court. The agency believes,

we submit that the courts serve as "collaborative 'instrumentalities of justice' and not business rivals" of the agency (*United States* v. *Ruzicka,* 329 U.S. 287, 295). The decision below disregards that scheme.

B. THE COURT OF APPEALS' CONCLUSION DENYING FDA JURISDICTION IS BASED ON ERRONEOUS PREMISES

The court of appeals rested its conclusion that FDA is without jurisdiction in all circumstances to adjudicate "new drug" status upon a series of erroneous premises: (1) that no procedure exists for agency consideration of the question; (2) that the agency should not be held to have the power to adjudicate "new drug" status because its determination would not be judicially reviewable; (3) that the structure of the Act compels the manufacturer to decide without benefit of an agency determination whether his product is a "new drug" and either market it without approval or concede such status by filing an NDA; and (4) that the inquiry into safety and efficacy undertaken when the agency acts upon an NDA is significantly different from that into "general recognition" of safety and efficacy underlying determination of "new drug" status. In our view, the court incorrectly assessed each of these factors, and none of them warrants the result it reached.

1. *The Agency May Determine "New Drug" Status in Proceedings Under Section 505 or in Declaratory Order Proceedings Under the Administrative Pro-*

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however, that it has primary jurisdiction over "new drug" status, safety and effectiveness, and it will continue to assert this position where appropriate.

cedure Act. It is our contention that the Third Circuit's decision in *CIBA Corporation* v. *Weinberger, supra* (No. 72–528), reflects the correct interpretation of the Act. There, the agency withdrew approval of an NDA held by CIBA for Ritonic Capsules. CIBA attacked the withdrawal in two separate judicial proceedings. It petitioned for review of the withdrawal order in the Second Circuit pursuant to Section 505 (h), and it filed a declaratory judgment action in a federal district court in New Jersey, claiming that its product is not now a "new drug" and therefore is exempt from the Act's requirements (J.A. 185–192). The district court dismissed the complaint (J.A. 214); the Second Circuit affirmed the agency's withdrawal order. *Ciba-Geigy Corp.* v. *Richardson,* 446 F.2d 466. On appeal from the dismissal of its district court action, CIBA contended in the Court of Appeals for the Third Circuit that neither the agency nor the Second Circuit on direct appeal of the agency's action, had jurisdiction to determine whether Ritonic Capsules are a "new drug" subject to the Act; rather, it claimed that it could litigate this issue in full in the district court. The Third Circuit held, however, that the agency necessarily is empowered to decide the threshold question as an incident of its power to approve or withdraw approval of NDAs and that its decision on that issue is reviewable in the court of appeals on direct appeal from the agency's order (J.A. 216):

> Inherent in the grant of administrative competency to conduct and decide new drug pro-

> ceedings is jurisdiction to decide whether the product in question in a given case is lawfully subject to such a proceeding. And, if the administrative agency takes jurisdiction, the same jurisdictional issue is present for judicial review on direct appeal from the administrative decision.
>
> In disapproving Ritonic Capsules the Commissioner and the Court of Appeals for the Second Circuit necessarily decided that the 1962 amendments of the Act were applicable to that product. * * * It is neither necessary nor appropriate that the District Court for the District of New Jersey entertain a separate suit by the loser in the administrative proceeding and in the direct appeal therefrom for a redetermination of the same question.

Under this approach, the agency serves as the primary forum for determining what is a "new drug" subject to its jurisdiction.

Of course *CIBA,* which correctly establishes the agency's subject-matter jurisdiction to deal with the "new drug" question, arose in the context of a proceeding for withdrawal of approval of an NDA. But even where the manufacturer has no NDA in effect or is not seeking approval for one, so that the determination of the "new drug" question would not be ancillary to any proceeding specifically prescribed by the Act, a procedure is available whereby the agency may determine the issue. The Administrative Procedure Act expressly enables FDA, like any other administrative agency, to issue "a declaratory order to terminate a controversy or remove uncertainty" (5

U.S.C. 554(e)). The present case illustrates an appropriate occasion for the exercise of the agency's declaratory order authority to resolve the controversy whether the respondent's drugs are in fact "me-too" copies of the products whose NDAs were withdrawn, and whether they are either effective or immune from the Act's efficacy requirements, by reason of the grandfather clause or otherwise. (A discussion of the appropriateness of initial agency consideration of these issues is set forth in point II, *infra*.)

An analogous situation was presented in *Frozen Food Express* v. *United States,* 351 U.S. 40, in which this Court held reviewable an order of the Interstate Commerce Commission determining that certain commodities were not exempt from regulatory requirements under the agricultural exemption to the Motor Carrier Act. The Court noted (351 U.S. at 44) that such an order is declaratory under the Administrative Procedure Act, rather than immediately coercive. Similarly, in *Red Lion Broadcasting Co.* v. *Federal Communications Commission,* 395 U.S. 367, 372–373, n. 3, which involved an application of the FCC's fairness doctrine, this Court ruled that since FCC could have conducted adjudicatory proceedings in which the licensee's compliance with the fairness doctrine would be an issue, "it could, under the Administrative Procedure Act, have issued a declaratory order in the course of its adjudication which would have been subject to judicial review."

Finally, FDA may, as in the case of over-the-counter drugs (see pp. 24–25, *supra*), promulgate pro-

cedures for rule-making under Section 701(a) (21 U.S.C. 371(a)) to classify categories of drugs as generally recognized as safe and effective, rather than dealing with each drug separately. Cf. *Abbott Laboratories* v. *Gardner*, 387 U.S. 136, 147, 149–152; *Ciba-Geigy Corp.* v. *Richardson*, 446 F. 2d 466 (C.A. 2), and authorities cited therein.

2. *Judicial Review of the Agency's "New Drug" Determination is Available.* Noting that the Act grants a right of direct appeal to the courts of appeals only from an order denying or withdrawing approval of an NDA (Section 505(h)),[11] the court below reasoned that "[i]t is not to be assumed that the Act confers an adjudicatory right on the Secretary from which no judicial review, however limited, is provided or allowed" (J.A. 268). But this is an erroneous premise. Review is available regardless of the form of order, so long as the order is administratively final.

If FDA's ruling on the threshold question of the Act's coverage is made in the context of an administrative proceeding that results in an order refusing (Section 505(d)) or withdrawing (Section 505(e)) approval of an NDA, that ruling is reviewable in the courts of appeals upon petition of the applicant-manufacturer under Section 505(h). Since that provision does not purport to limit the kinds of issues

[11] Section 505(h), J.A. 480, provides in part: "An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals * * * a written petition praying that the order of the Secretary be set aside. * * *"

the courts of appeals may consider in reviewing the agency's denials or withdrawals of approvals, the agency's determination of the threshold question whether the product involved is lawfully subject to the agency proceeding is, as the Third Circuit held in *CIBA,* subject to judicial review on direct appeal.

On the other hand, if the agency's order is not a denial or withdrawal within the court of appeals' jurisdiction under Section 505(h), but is instead an order declaring "new drug" status, it may be reviewed in the district court under the Administrative Procedure Act.[18] See *Citizens to Preserve Overton Park* v. *Volpe,* 401 U.S. 402; *Abbott Laboratories* v. *Gardner, supra; Frozen Food Express* v. *United States, supra.* That Act specifically provides that "final agency action for which there is no other adequate remedy in a court [is] subject to judicial review." 5 U.S.C. 704.

In *Abbott Laboratories,* drug manufacturers challenged FDA regulations prescribing certain labeling requirements for prescription drugs under Section 701(a) of the Act, 21 U.S.C. 371(a). Unlike regulations under Section 701(e) of the Act, which are subject, under Section 701(f), to direct review in the court of appeals (21 U.S.C. 371(f)), the Act provides no special procedure for review of such regulations. The government contended that the direct review procedure was exclusive and that other types of regulations were therefore unreviewable. This Court held that the provisions for direct review "were simply

[18] Jurisdiction in the district court to review the order would be based on 28 U.S.C. 1331 or 28 U.S.C. 1337.

intended to assure adequate judicial review of such agency decisions, and that their enactment does not manifest a congressional purpose to eliminate judicial review of other kinds of agency action." *Abbott Laboratories* v. *Gardner, supra,* 387 U.S. at 144. That review, the Court ruled, is available under the Administrative Procedure Act, 5 U.S.C. 701–704, and under the Declaratory Judgment Act, 28 U.S.C. 2201, so long as the agency's action is final and ripe for consideration. Compare *Toilet Goods Assn.* v. *Gardner,* 387 U.S. 158. Thus, under the rationale of *Abbott Laboratories,* (1) any manufacturer whose NDA is denied or withdrawn by the agency, may obtain direct review in the court of appeals under Section 505(h), including review of his product's "new drug" status; and (2) a final declaratory order by the agency, including any final declaratory determination of "new drug" status not otherwise within the direct review provisions of the Act, may be reviewed in the district court under the Administrative Procedure Act.

3. *The Act Does Not Compel the Manufacturer to Concede "New Drug" Status When Filing an NDA.* The court below attempted to buttress its conclusion that the agency may not determine its own jurisdiction by contending that the question of "new drug" status is never presented when an application for approval is filed. It reasoned that "[t]he very filing of the application is a concession and recognition by the applicant-manufacturer that the article is a 'new drug'" (J.A. 268). However, the source of this conclusion is not readily apparent. Nothing in the Act compels a

manufacturer who is uncertain whether its product is a "new drug" to choose between marketing the product without administrative approval, thus risking civil and criminal penalties, or making what the court below characterizes as a "concession" that the product falls within the Act by filing for approval under Section 505(b). Instead, the manufacturer may file a request for a determination that its product is not a "new drug," under the declaratory order procedures of the Administrative Procedure Act, and offer evidence in support of its contention."

An order making such a determination, or a general rule doing so for a class of drugs (see pp. 24–25, *supra*), becomes the basis on which the manufacturer orders his affairs. If FDA determines that the product is not a "new drug," it may be marketed without an approved NDA; if the agency determines that it is a "new drug" subject to the regulatory requirements of the Act, the manufacturer may pursue an application for approval before the agency, withdraw the product from the market in order to avoid the substantial civil and criminal sanctions against unauthorized products, or, where feasible, reformulate and relabel the product to bring it within a class of drugs generally recognized as safe and effective. Cf. *Frozen Food Express* v. *United States*, *supra*.

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[11] Since 1942, the agency, considering it had authority to determine "new drug" status, has issued opinions to manufacturers that particular drugs are or are not "new drugs." See pp. 6, 9, *supra*. Since "new drug" status is a jurisdictional question, the absence from the agency's application form of a space in which to raise the issue cannot be controlling, as the court below seems to have believed (J.A. 268).

One apparent difficulty with the reasoning of the court below is that, even if the manufacturer "concedes" that his product is a new drug by filing for approval, the agency's "acceptance" of this concession could not settle the jurisdictional question. Assuming the court is right that the agency is without power to decide the question, then if the agency denied the application or subsequently withdrew its approval, the court of appeals on review would either have to determine the "new drug" question *de novo* [50] or render a decision whose jurisdictional basis under the Act would be subject to relitigation in a district court action for declaratory judgment.[51]

4. *The "New Drug" Issue and the Safety and Effectiveness Issues Raise Substantially Similar Questions.* Finally, the court of appeals erred in relying (J.A. 268–269) for its conclusion upon the differences it perceived between the safety and effectiveness questions involved in an agency proceeding for approval or withdrawal of approval of an NDA (under Sections 505(d) and 505(e)), on the one hand, and the questions of "general recognition" of safety and effectiveness involved in the "new drug" determination (under Section 201(p)), on the other. In our view, the inquiry in either case is substantially similar, with resolution of the question turning upon expert scientific and medical judgment.

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[50] This would be a highly unusual procedure, since courts of appeals are not equipped to resolve factual issues *de novo*. Cf. 28 U.S.C. 2347(b).

[51] This is, in substance, petitioner's contention in *CIBA Corporation* v. *Weinberger*, *supra*, No. 72–528.

Thus, under the elaborate safety and effectiveness criteria spelled out in Section 505(d), the agency is expressly authorized to deny an application if it concludes that it has insufficient information to determine whether the drug is safe and effective for use by humans under the conditions prescribed. If the agency properly reaches such a conclusion, it would be a rare case indeed in which there could at the same time exist proper general recognition of safety and effectiveness sufficient to eliminate agency jurisdiction over the product under the "new drug" definition.

Furthermore, Section 505(d) directs FDA to deny approval where there is a lack of "substantial evidence" of effectiveness, which is defined in terms of clinical investigations "by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts * * * " that the drug will be effective as claimed. This basic theme of judgment by qualified experts precisely echoes Section 201(p)'s definition of a "new drug" as one "not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use * * *." Under both provisions of the Act, therefore, the emphasis is on the expert knowledge and experience of scientists based upon carefully controlled clinical experimentation and backed by substantial support in scientific literature. Cf. *United States* v. *An Art. of Drug "Bentex Ulcerine"*, 469 F. 2d 875, 880 (C.A. 5). The substantial over-

lap in the content of the inquiries reinforces the conclusion that the regulatory scheme established by Congress encompasses administrative authority to make both sorts of determinations.[82]

Indeed, it is the position of FDA that as a general proposition there can be no general recognition of safety and effectiveness by experts where "substantial evidence" of effectiveness as defined by Congress is lacking. In other words, the kind of scientific support for claims of efficacy required to obtain approval of an NDA is generally a necessary condition to avoidance of "new drug" status (although not necessarily a sufficient condition, since a drug can be proved efficacious without there being a general recognition of this fact), so that a major part of the inquiry under both Section 201(p) and Section 505(d) is precisely the same.[83] See p. 12, *supra*.

C. THIS COURT HAS IN OTHER CONTEXTS RECOGNIZED THE BROAD POWERS OF ADMINISTRATIVE AGENCIES TO DETERMINE THEIR OWN JURISDICTION

The fact that Congress has not spelled out in so many words the authority of FDA to pass upon the question whether a product is a "new drug" does not mean it should be held to have excluded the agency

[82] Of course, we do not deny that in enforcement proceedings the district court must decide whether a product is a "new drug" subject to regulation, at least where the issue has not been litigated before the agency. See, *e.g.*, *Bentex Ulcerine*, *supra*. But the existence of such power in the courts is not inconsistent with its existence in the agency.

[83] The correctness of FDA's position on this issue is before the Court in connection with a companion case, *Hynson, Westcott and Dunning, Inc.* v. *Weinberger*, No. 72-414, and it will be briefed more fully there.

from the exercise of a function for which it is inherently well suited and which is vital to the effective administration of its responsibilities. Denial of the power to pass upon questions of "new drug" status would prevent FDA from dealing administratively with the problems presented by "me-too" copies of drugs whose NDAs have been withdrawn on efficacy grounds.[84] It would seriously undermine FDA's program of reviewing the status of and establishing standards for over-the-counter drugs. And it would crowd the courts with a large volume of litigation requiring *de novo* resolution of complex scientific issues. In a situation such as this, the Court, in the absence of an explicit Congressional directive, should inquire where Congress would prefer to have questions of this nature determined. We submit that the sensible answer is the expert administrative agency. That is how the Court has answered similar questions in the past.

Thus, in areas in which economic regulation has been to some degree applied ~~on~~ to an industry, expert administrative agencies have been held to possess broad powers to determine the scope of their own jurisdiction. Indeed, this Court has said that it may not, "in the absence of compelling evidence that such was Congress' intention, * * * prohibit administrative action imperative for the achievement of an agency's ultimate purposes." *Permian Basin Area*

[84] This assumes that the Court will agree with the government's position in the *USV* case (No. 72-666) that the grandfather clause does not exempt "me-toos" from the efficacy requirements of the Act.

Rate Cases, 390 U.S. 747, 780; cf. *United States* v. *Southwestern Cable Co.,* 392 U.S. 157; compare *National Broadcasting Co.* v. *United States,* 319 U.S. 190, 219, 220; *American Trucking Assns.* v. *United States,* 344 U.S. 298, 311.

This Court has recently observed that, where the question of an agency's threshold jurisdiction turns on the resolution of technical questions of fact of a kind arguably within the competence of the agency, it "should at least be requested to institute proceedings." *Ricci* v. *Chicago Mercantile Exchange,* No. 71-858, decided January 9, 1973 (slip op., p. 15). Even where it is claimed that administrative jurisdiction is lacking because a product is not being sold in commerce, the question is ordinarily to be resolved in the first instance by the agency. *Myers* v. *Bethlehem Corp.,* 303 U.S. 41, 50–51. Cf. *Oklahoma Press Pub. Co.* v. *Walling,* 327 U.S. 186, 210–211. "Authority to investigate the existence of violations accordingly include[s] authority to investigate coverage." *Id.* at n. 47. Similarly, the Court has held that whether a union is a "labor organization" *arguably* within the jurisdiction of the NLRB, or whether an electric system is subject to regulation by the FPC, are jurisdictional questions to be decided in the first instance by the agency. *Marine Engineers Beneficial Assn.* v. *Interlake S. S. Co.,* 370 U.S. 173, 185; *Federal Power Commission* v. *Louisiana Power & Light Co.,* 406 U.S. 621, 647.

No sound reason appears why Congress would deny this type of essential authority to an agency with

sweeping responsibilities for protecting the public health, while allowing it to agencies engaged in economic regulation. The statutory scheme of the Federal Food, Drug and Cosmetic Act shows that Congress did not so intend. Rather, in conferring on the agency comprehensive powers to perform its mission, it necessarily included the threshold power to decide whether products are "new drugs" over which it has jurisdiction.

II. THE DISTRICT COURT PROPERLY EXERCISED ITS DISCRETION IN REFERRING TO FDA THE QUESTION WHETHER RESPONDENTS' PRODUCTS ARE "NEW DRUGS" REQUIRING ADMINISTRATIVE APPROVAL

Since FDA has power to decide the "new drug" question, the court of appeals erred in setting aside the district court's referral of that question to the agency. The district court's referral was an appropriate exercise of the broad equitable discretion vested in the courts in declaratory judgment actions, and was in accordance with the principle that technical questions unsuited for judicial determination should, where possible, be resolved in the first instance by the appropriate regulatory agency.

The wisdom of the referral is apparent from examination of the issues raised in the declaratory judgment proceeding. Following the NAS–NRC finding of ineffectiveness, the agency here made an administrative determination that there is no substantial evidence that drugs containing pentylenetetrazol are effective. It therefore withdrew NDAs that had been approved prior to 1962, when safety had been the

sole criterion. This determination was not appealed and thus became final. However, the action directly affected only the three NDAs that were outstanding for products containing this drug. Many other manufacturers had products on the market that appeared, in FDA's view, to be mere copies of the drugs found ineffective. Since these "me-too" drugs had never been through the NDA process, there was no physical piece of paper for FDA to withdraw. But, in FDA's view, if these were in fact substantially the same drugs and were as ineffective as the pioneers, Congress wanted them removed from the market too.

After the respondents here had declined to participate in the NDA withdrawal proceedings and had been advised by letter from FDA that the agency, after the withdrawal of approval had become final, considered their products containing pentylenetetrazol to be "new drugs" that could not be marketed without an approved NDA, respondents brought this declaratory judgment action. They contended (1) that their products are not now "new drugs," and (2) that they are exempt from the efficacy requirements of the 1962 amendments by reason of the grandfather clause in Section 107(c)(4). J.A. 223–224. The factual issues presented vary somewhat depending on whether the government's interpretation of the grandfather clause and the "new drug" definition or that of the manufacturers is accepted, but, in either event, they are the kind of issues particularly suited to initial determination by the expert administrative agency.

The district court concluded that even though the "new drug" determination "can be made in this forum, the nature of the proof relevant to that issue makes the F.D.A. the more able arbiter of the question. * * * Evaluation of conflicting reports as to the reputation of drugs among experts in the field is not a matter well left to a court without chemical or medical background" (J.A. 256–257). It thus carefully explained its reasons for referring the matter to the agency. In contrast, the court of appeals noted respondents' claims concerning the differences between their own and the disapproved products but characterized them as only "questions of fact not relevant to the simple question of jurisdiction" (J.A. 264, n. 18).

The entire question of jurisdiction is not simple, however. For example, under the government's view of Section 107(c)(4),[35] a "me-too" product is considered "covered by" the "pioneer's" NDA, and therefore not grandfathered, if it is identical to or substantially similar or closely related to the pioneer in the chemical composition of one or more of its active components. If this view is correct, a factual issue arises whether respondents' products are in fact "me-toos." Here, the respondents have denied that their drugs are like the products whose NDAs were withdrawn, distinguishing them on the basis that the

[35] The government's position on the correct interpretation of the grandfather clause will be fully briefed and argued in two companion cases to the instant case, *Hynson* (No. 72–414) and *USV* (No. 72–666), which squarely present various aspects of the issue.

latter are intravenously administered or are a compound containing the additional ingredient reserpine.

Even if the government's interpretation of the grandfather clause were to be rejected, a factual issue arises whether, under clause (B) of Section 107(c)(4), respondents' products were generally recognized by qualified experts as safe in October 1962, or, under an alternative claim of current "old drug" status, whether they are today generally recognized by such experts as both safe and effective. As pointed out in point I(B)(4), *supra,* pp. 55–57, the resolution of such technical factual issues substantially overlaps the type of inquiry routinely undertaken by FDA in passing on NDAs.

Since these kinds of questions require determination of highly complex chemical, medical and pharmacological questions, which turn on expert evaluation of the state of scientific opinion and knowledge as to the products involved, they may appropriately be referred to expert agencies by a court. For as this Court recently observed, even "[w]hen there is a basis for judicial action, independent of agency proceedings, courts may route the threshold decision as to certain issues to the agency charged with primary responsibility for governmental supervision or control of the particular industry or activity involved." *Marine Terminal Association* v. *Rederi Transatlantic,* 400 U.S. 62, 68. This is merely an application of well established principles recognizing the specialized role of administrative agencies like FDA. As this Court observed in *Far*

East Conference v. *United States*, 342 U.S. 570, 574-575:

> * * * in cases raising issues of fact not within the conventional experience of judges or cases requiring the exercise of administrative discretion, agencies created by Congress for regulating the subject matter should not be passed over. This is so even though the facts after they have been appraised by specialized competence serve as a premise for legal consequences to be judicially defined. Uniformity and consistency in the regulation of business entrusted to a particular agency are secured, and the limited functions of review by the judiciary are more rationally exercised, by preliminary resort for ascertaining and interpreting the circumstances underlying legal issues to agencies that are better equipped than courts by specialization, by insight gained through experience, and by more flexible procedure.

This Court's recent decision in *Ricci* v. *Chicago Mercantile Exchange, supra,* directly supports the district court's decision to refer the "new drug" issue to FDA. That case, like this one, involved a claim for exemption from a statute. It was a private treble damage action under the Sherman Act in which the defendant claimed exemption from the antitrust laws on the ground that its conduct was justified by the requirements of a regulatory statute, the Commodities Exchange Act. This Court held that the exemption issue must be decided by the district court, but that in making this determination the trial judge should first refer the

case to the regulatory agency charged with administering the Commodity Exchange Act. Such a referral, this Court held, would be of material aid to the district court in determining the exemption issue, because that issue turns on questions of fact "that should be dealt with in the first instance by those especially familiar with the customs and practices of the industry and of the unique market place involved. * * * They are matters typically lying at the heart of an administrative agency's task * * *" (slip op., p. 16).

The present case is an even stronger one than *Ricci* for referral to the agency. The issue before the district court in the declaratory judgment proceeding concerns a claim for exemption from the requirements of a statute. This claim is based, not on a purported conflict of one statutory regime with another, as in *Ricci*, but on disputed interpretation of the language of the regulatory statute itself. Resolution of these questions turns on technical issues of the kind normally left for expert administrative resolution. The agency has not considered, in an administrative proceeding, the specific claims respondents made in the district court, because respondents never presented them to it. By affording respondents an opportunity to be heard on their claims before the agency, the district court has also given the agency the opportunity to reconsider its views respecting the marketability of respondents' drugs. If respondents' submission to the agency persuades it to alter its initial determination, there will be no need for further judicial consideration. If it does not, then the agency's decision with

respect to these particular drugs will provide a more solid footing for judicial consideration of the issues that remain in controversy. Cf. *Far East Conference* v. *United States, supra,* 342 U.S. at 574–575.

Thus the district court's referral to the agency of the "new drug" and grandfather issues was a reasonable and desirable accommodation of the functions of court and agency, wholly consistent with the flexible nature of the declaratory judgment remedy. Cf. *Kerotest Mfg. Co.* v. *C–O–Two Co.,* 342 U.S. 180, 183–184.

CONCLUSION

For the foregoing reasons the decision of the court of appeals should be reversed.

Respectfully submitted.

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